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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEA, CHRISTOPHER RAYMOND	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,320	SEN ET AL.	
	Examiner	Art Unit	
	Christopher R. Lea	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/2006 & 5/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/IN04/00306.

Claims 1-56 are pending. Claims 1-56 are under examination.

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

2. The information disclosure statement(s) (IDS) submitted on March 31 and May 11, 2006, were filed before the mailing date of the first office action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Any references not complying with 37 CFR 1.98 have been lined through and reason for non-compliance given on the form.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 5-15, & 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims contain reference to "pharmaceutically acceptable derivatives" of lamivudine, zidovudine, and NNRTIs in general (specifically nevirapine and efavirenz). It is unclear which type compounds are encompassed by the term derivative as salts, isomers, analogues, metabolites/prodrugs, crystals/polymorphs, solvates/hydrates or combinations thereof may be embrace by the term derivative and the specification does not describe any such derivatives so as to reasonably convey to the skilled artisan that the inventors had possession of the claimed composition containing any of such derivatives.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-44 & 50-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1, 5-15, & 36 recite the term "derivative" is indefinite. The term derivative does not set forth in full, clear and exact terms the identity and location of modifications to the compound that would be considered to fall within the metes and bounds of the claim. Since claims 2-4, 16-35, & 37-44 are ultimately depend from claim 1, they have been rejected under 35 U.S.C. 112 second paragraph as well.

8. Regarding claims 16, 19, 22, 28, 34, 36, 37, & 43, the phrase "and the like" renders the claim(s) indefinite because the claim(s) include(s) elements not actually

disclosed (those encompassed by "and the like"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

9. Regarding claims 50-53, the claims recite nevirapine as a possible component ("nevirapine or efavirenz") but then claim the amount of nevirapine to be delivered. This appears to make nevirapine a required component of the method, which is internally inconsistent with the claims, hence, the metes and bounds of the claims are indefinite as it is unclear whether nevirapine is required or not.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sen et al. (WO 03/090762) in view of Conte et al. (US Patent 5,681,583) or Cooper et al. (US Patent 2,887,438) as witnessed by Maenza et al. (American Family Physician, June 1998, 57(11), p. 2789-98) and Straszewski et al. (New England journal of Medicine, December 1999, 341(25), 1865-73).

Applicant claims

Applicant claims a two-part antiretroviral pharmaceutical composition comprising a controlled release formulation and an immediate release formulation. The controlled release formulation comprises lamivudine, zidovudine, a pharmaceutically acceptable calcium salt, and a mixture of hydrophilic polymers selected from the group consisting of cellulose ethers, polyuronic acids, pharmaceutically acceptable gums and mixtures thereof. The immediate release formulation comprises a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) drug (specifically nevirapine and efavirenz) and pharmaceutically acceptable excipients. Applicant further claims the composition in the form of a bi-layer tablet or a core-shell tablet.

Determination of the scope and content of the prior art (MPEP 2141.01)

Sen et al. teach, as a whole, a controlled release formulation containing lamivudine and zidovudine.

Claims 1-8 & 36-44: Sen et al. teach a controlled release formulation comprises lamivudine, zidovudine, a pharmaceutically acceptable calcium salt, and a mixture of hydrophilic polymers selected from the group consisting of cellulose ethers, polyuronic acids (alginates), pharmaceutically acceptable gums and mixtures thereof (abstract; page 9, lines 18-28; and claim 1). Sen et al. list possible antiretroviral drugs that may be used with the composition including nevirapine and efavirenz (page 11, lines 1-3).

Claims 9 & 10: Sen et al. teach the amount of lamivudine to be contained in a dose of the composition is 300 mg (page 9, lines 30-32 and claim 3).

Claims 11 & 12: Sen et al. teach the amount of zidovudine to be contained in a dose of the composition is 600 mg (page 9, lines 30-32 and claim 5).

Claim 13-15: Sen et al. list possible antiretroviral drugs that may be used with the composition including nevirapine and efavirenz (page 11, lines 1-3). Determination of the therapeutically effective amount of a drug is within the purview of the skilled artisan. Additionally, Maenza et al. teach the daily dosage of nevirapine is 400mg (table 1) and Straszewski et al. teach the daily dosage of efavirenz is 600 mg (abstract).

Claims 16-18: Sen et al. teach that hydroxypropyl methylcellulose is the preferred cellulose ether and can be present in an amount of 3-8% in the formulation (page 15, lines 1-18 and claim 10).

Claims 19-21: Sen et al. teach that sodium alginate is the preferred polyuronic acid and can be present in an amount of 1-6% in the formulation (page 15, lines 1-18 and claim 10).

Claims 22-24: Sen et al. teach that guar gum is the preferred pharmaceutically acceptable gum and can be present in an amount of 0.5-6% in the formulation (page 15, lines 1-18 and claim 10).

Claims 25-27: Sen et al. teach that calcium sulfate is the preferred pharmaceutically acceptable calcium salt and can be present in an amount of 0.1-1.2% in the formulation (page 10, lines 21-23 and claim 10).

Claims 28 & 29: Sen et al. teach that the formulation comprises at least one water dispersible or water soluble diluent selected from amongst microcrystalline cellulose, dicalcium phosphate, lactose, and starch (page 16, line 27 through page 17, line 7 and claim 17).

Claims 30 & 31: Sen et al. teach that microcrystalline cellulose is the diluent and can be present in an amount of 5-20% in the formulation (page 16, line 27 through page 17, line 7 and claim 19).

Claims 32 & 33: Sen et al. teach that dicalcium phosphate is the diluent and can be present in an amount of 1-5% in the formulation (page 16, line 27 through page 17, line 7 and claim 21).

Claims 34 & 35: Sen et al. teach that the formulation may contain a lubricant such as talc, stearic acid and magnesium stearate in an amount of 0.2-3% (page 17, lines 16-20).

Claims 45-48, 55, & 56: Sen et al. teach a process for preparing a pharmaceutical composition comprising mixing lamivudine and zidovudine with the release retarding excipients (e.g. HPMC, sodium alginate and guar gum) and a calcium salt to form a blend and then compressing the blend to form tablets (claim 42). Sen et al. also teach dry and wet granulation techniques for blending prior to compression (claims 43 & 44).

Claims 49-54: The methods claimed in claims 49-54 are either necessarily carried out by the compositions claimed in claim 1 or the claimed results are within the purview of the skilled artisan to attain through the determination of the therapeutically effective amounts of the drugs to be delivered. Sen et al. teach that the high pill burden may be alleviated if a once daily form of the drug regimen was available (page 8, lines 1-5) and that the blood plasma level of the drugs may be controlled based on the formulation of the composition (page 8, lines 13-19).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The difference between the teachings of Sen et al. and the instant claims is that Sen et al. does not teach the bi-layer or core-shell tablet form of the composition. This deficiency in Sen et al. is cured by the teachings of Conte et al. or Cooper et al.

Conte et al., teach as a whole, a bi-layer tablet with one layer being a controlled release layer and the other an immediate release layer.

Claims 3, 5, 7, 45, 47, & 48: Conte et al teach a solid pharmaceutical composition for oral administration, comprising: at least one first layer consisting

essentially of a first active material and a disintegrating or superdisintegrating compound (immediate release) and at least one second layer located on said first layer containing a portion of said first active material or a second active material and an excipient or adjuvant that retards disintegration (controlled release); said active material in said first layer being released upon administration to a host at a rate faster than the rate of release of said active material in said second layer (claim 1)

Claim 36: Conte et al. teach the immediate release layer comprises 1-90% active agent (claim 22) and specifically teach an example containing about 50% active agent (example 1, column 6).

Claims 37-44: Conte et al. teach that the immediate release layer comprises microcrystalline cellulose (which is a type of powdered cellulose), calcium phosphate, lactose, starch, mannitol, sodium carboxymethylcellulose, pregelled starch, cross-linked polyvinylpyrrolidone (crospovidone), magnesium stearate, stearic acid and colloidal silica (silicon dioxide) as adjuvants/excipients (claims 1, 4, & 6). Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (See MPEP § 2144.05 II).

Cooper et al., teach as a whole, a table having a controlled release core and an immediate release shell.

Claims 4, 6, 8, 46, 55, & 56: Cooper et al. teach "a method for preparing accurate prolonged-action dosage unit forms for oral administration. [The] method comprises the preparation of a core, having evenly and thoroughly distributed therein an accurate amount of a therapeutic ingredient together with a mixture of substances which are non-absorbable from the gastro-intestinal tract but which, when compounded in the manner described below, are capable of releasing the therapeutic substance slowly over an extended period of time. Around this core there is then compressed, by suitable mechanical means, a layer of the therapeutically active ingredient in admixture with a sufficient quantity of excipients, binders and lubricants to obtain a tablet of suitable size and hardness." (column 1, line 64 through column 2, line 5).

Finding of *prima facie* obviousness
Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the formulation controlled release formulation taught by Sen et al. as the controlled release portion of the tablet taught by either Conte et al. or Cooper et al. and produce the instant invention. Further, it would have been obvious to add another antiretroviral drug to the tablet since both Maenza et al. and Straszewski et al. teach treating HIV with combination drug therapy, and the determination of release type (controlled or immediate) for each drug is within the purview of the skilled and largely dependent on the drug's plasma half-life. The skilled artisan would have been motivated to make a tablet having controlled and immediate release of combination of antiretroviral drugs because Sen et al. teach that patient

compliance is improved when the dosing scheme is simplified preferably to a once-a-day oral form (page 8, lines 1-5).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in making a tablet having controlled and immediate release of combination of antiretroviral drugs and producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Conclusion

Claims 1-56 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher R. Lea whose telephone number is (571) 270-5870. The examiner can normally be reached on Mon-Thu 7:30-5:00 ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571)272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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CRL

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616